DETAILED ACTION

Response to Restriction Requirement

Applicant's election of claims 9-14 in the reply filed on 1/22/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of Claims

Claims 1-26 are submitted, Claims 1-8 and 15-26 are withdrawn and claims 9-14 are pending in this office action based on elected group. See above.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/15/06 is acknowledged and has been reviewed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating dogs with atrial fibrillation (AF) with a statin, does not reasonably provide enablement for preventing AF with a wide variation of statins. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

In the instant case, applicants are claiming in part, a method of preventing a AF in a mammal (claim 9), administering a therapeutically effective amount of the compound of a statin drug.

Nature of the invention.

The nature of the invention is directed to method of preventing AF in a mammal/human comprising administering a statin drug. The nature of the claim is such that prevention of AF is achieved after administration of a statin to the patient in need thereof.

According to St Jude, there not all AF are preventable from occurring. The best prevention, however, is a life-long commitment to physical activity, good nutrition etc as taught. See reference in its entirety.

State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is very complex because of its serious complications or implications with heart failure, angina, peripheral embolism and stroke. It is very crucial for the skilled artisan to be able to detect AF. As taught treatment of AF is currently the subject of many controversies, and can be divided depending on whether it is acute or chronic and is based on two main objectives, namely restoration of sinus rhythm (and hence of atrial contraction) and control of heart (ventricular) rate. We should never forget that at the same time we are trying to treat AF we are always looking for a reversible cause that should be treated and for preventing the thromboembolic complications related to it thus making this very difficult to even treat let alone prevent. See enclosed ref. Saad, Current Trends in the treatment of AF, Feb 2007 underlined sec.

The existence of these implications such as different cardiac and systemic disorders, the most common being coronary heart disease, hypertension, cardiomyopathies, vauvular heart desease, thyrotoxicosis, acute infections, excess alchool intake, pulmonary thromboembolism, lung carcinoma, postoperative problems and the idiopathic form establishes that the contemporary knowledge in the art would prevent one skill in the art from accepting any therapeutic regimen on its face.

The nature of the invention is not only to prevention but to the use of any statin drug for prevention of AF. This recites a very wide range of statins which may or may not render the patient a positive result. The nature of the invention is very broad, and the relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of proliferative and inflammatory diseases. Each particular AF with is complication need to be carefully taken into consideration as the disease has its own specific characteristics and etiology.

As taught by Adabag "among the 13783 patients, 5417 (39%) received statin treatment. Statin-treated patients were younger with fewer comorbid conditions. After propensity adjustment, the baseline characteristics of the statin-treated and untreated patients were similar. During an average follow-up of 4.8 years, 1979 (14%) patients developed AF. In the overall study population there was no difference in AF incidence with statin treatment (hazard ratio 1.0, 95% CI 0.88- 1.14, *P* = .9). However, AF was less common among statin-treated patients with CHF (hazard ratio 0.57, 95% CI 0.33-1.00, *P* = .04).

Conclusions: We did not find any effect of statin treatment on AF incidence in patients with CHD; however, AF was reduced in a subset of patients with CHF.

Also as taught recently by Howard et al. "while the current evidence evaluating the use of statins to prevent POAF is encouraging, definitive conclusions cannot be drawn. However, because statins are widely used in cardiac patients for other indications and are not associated with the risks inherent to antiarrhythmic drugs, their value as an adjunct to current preventive strategies for POAF deserves further study".

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection the

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with

a known or disclosed correlation between function and structure, or some combination of such characteristics.

In particular, the specification as original filed fails to provide sufficient written bases of any of the agents demonstrating wherein possession of use of the broad term statin drug. The mere fact that Applicant may have discovered one or atleast a few types of statin drugs to be effective in treating atrial fibrillation is not sufficient to claim the entire genus. For Example, simvastatin and lovastatin when administered to patient developed rhabdomyolsis. See enclosed journal article of Medical Sciences underlined sec. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between members of the genus is permitted. Concise structural features that could distinguish structures or compounds within the genus from others is missing from the disclosure.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species

to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11 and 13-14 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recite the limitation "a therapeutically effective amount" which is a relative term. The effective amount is different for a different mammal. For example, a therapeutically effective amount for small mammal may not be a therapeutically effective amount for larger mammal, for example. The scope of a therapeutically effective amount is unclear and confusing. Thus, any amount would be encompassed by the unclear scope of the Claim 9. Appropriate clarification is required.

Claim12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites “a method as defined in claim" but failed to indicated what claim or claims is/are referred to.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 9-10 and 13-14 are rejected under 35 U.S.C. 102(a) as being anticipated by West et al. J. Hypertension, 2002, 20:2513-2517.

The reference teaches administering a statin (pravastatin or simvastatin) to patients with atrial fibrillation wherein the patient is a mammal-human. See underlining pages of document in its entirety.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over West et al. J. Hypertension, 2002, 20:2513-2517 in view of Hanson US 6,376,242 taken with Ullah et al., US 6,235,311.

West is applied here as above.

Hanson teaches administering statins such as atorvastatin, cerivastatin simvastatin etc to humans and mammals suffering from atrial fibrillation and cardiovascular disease. See col. 3, line 50, col. 10, lines 56—60, col. 12, line 64 and col. col. 35, lines 37-40. The reference further teaches the drugs are administered at 0.01-30 mg/kg/day, see col. 42, lines 15-16.

Ullah et al. teach administering a statin such as pravastatin, atorvastatin, simvastatin, lovastatin and cervastatin to reduce the risk of or treating cardiovascular event or disease including coronary artery disease. See col. 1, lines 58-65 and col. 2, lines 48-50. It is understood by the Examiner that AF results in cardiovascular event such as stroke, heart attack.

It would have been obvious to one of ordinary skill in the art to combine the cited references and administer a statin such as atorvastatin, simvastin or pravastatin to a patient suffering from atrial fibrillation because it is taught in the art that these drugs have been associated with 25-30% reduction in stroke rate in a patient. Since AF is a risk factoe of stroke it would have been obvious to administer a statin to reduce a coronary heart disease. See West underlined page 2513 where two types of statins used show reduction. Also the same statins hare used by Ullah et al, therefore one of

ordinary skill in the art would have been motivated to administer a statin in the event of atrial fibrillation.

No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
4/3/08

/Ardin Marschel/
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